Stability analysis and exit problem formulation in a 2D model for general anesthesia

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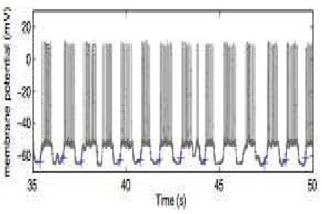
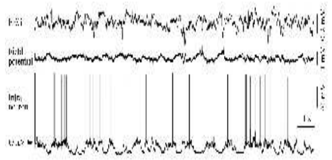
Bistability in anesthesia



Wilson *et al.* (2010), J Biol Phys 36: 245-259



Ferron *et al.* (2009), J Neurosci 29(31): 9850-9860

Hutt & Longtin (2009) model with no delay nor spatial dimension: a neural population model

Differential form, using the scaled (dimensionless) time $\tau = \sqrt{\alpha_1\alpha_2}t$:

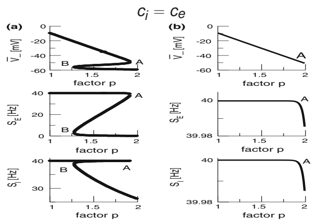
$$
\begin{aligned}
(\partial^2/\partial\tau^2 + \gamma_i\partial/\partial\tau + \omega_i^2)(V_i - V_e^r) &= a_i f(p)\omega_i^2 S_i(V_e - V_i - \theta_i) + \sqrt{2}\sigma \dot{W}_i \\
(\partial^2/\partial\tau^2 + \gamma_e\partial/\partial\tau + 1)(V_e - V_e^r) &= a_e S_e(V_e - V_i - \theta_e) + \sqrt{2}\sigma \dot{W}_e
\end{aligned}
$$

with $\gamma_i = (\beta_1+\beta_2)/\sqrt{\alpha_1\alpha_2}$, $\gamma_e = \sqrt{\alpha_1/\alpha_2} + \sqrt{\alpha_2/\alpha_1}$, $\omega_i = \sqrt{\beta_1\beta_2/(\alpha_1\alpha_2)}$. V_i, V_e are the PSPs at excitatory neurons, V_e^r the resting membrane potential, $\theta_i < \theta_e$ the threshold potentials of the pre-synaptic cells, S_e and S_i are sigmoids functions $S_k(x) = \frac{S_{max}}{1+e^{-c_k(x-\theta_k)}}$, $k \in \{i, e\}$ and a_k stand for the synaptic efficacies. W_k represent Wiener processes. $\alpha_1, \beta_1, \alpha_2, \beta_2$ define the mean synaptic response functions h_k:

$$
\begin{aligned}
h_i(t) &= a_i f(p)\frac{\beta_1\beta_2}{\beta_2-\beta_1}(e^{-\beta_1 t} - e^{-\beta_2 t}) \\
h_e(t) &= a_e \frac{\alpha_1\alpha_2}{\alpha_2-\alpha_1}(e^{-\alpha_1 t} - e^{-\alpha_2 t})
\end{aligned}
$$

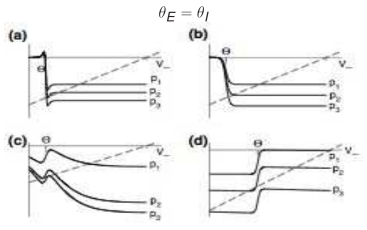
Finally, $f(p) = r^{-r/(r-1)}(rp)^{rp/(rp-1)}$ mimics the inhibitory action of the propofol p level, with $r = \beta_2/\beta_1$, $\beta_1 = \beta_0/p$

Bifurcation diagrams of Hutt & Longtin (2009) model



(a) A triple solution case: $\theta_E > \theta_I$

(b) A single solution case: $\theta_E = \theta_I$



(a) $c_e < c_i$ (b) $c_e = c_i$ (c) $c_e > c_i$ (d) $c_e >> c_i$

Adapted from Hutt A. and Longtin A., *Cognitive Neurodyn.* 4(1): 37-59, 2009.

Complexity reduction: a first-order system and a Heaviside rate function

$\alpha_1 \ll \alpha_2$ and $\beta_1 \ll \beta_2 \to r \gg 1 \to f(p) \approx p$, leads to 1st-order Langevin (SDE) equations. Besides, replacing S_k by a Heaviside function $S_k = \Theta(V_e - V_i - \theta_k)$, the system equations read:

$$
\begin{aligned}
\dot{V}_i &= -\beta(V_i - V_e^r) + \beta a_i p S_{max}\Theta(V_- - \theta_i) + \sqrt{2}\sigma\dot{W}_i \\
\dot{V}_e &= -\alpha(V_e - V_e^r) + \alpha a_e S_{max}\Theta(V_- - \theta_e) + \sqrt{2}\sigma\dot{W}_e
\end{aligned}
$$

where $\beta = \beta_1$ and $\alpha = \alpha_1$. The equation can also be split in three domains with a linear dynamics:

- Domain I: $V_e < V_i + \theta_i$

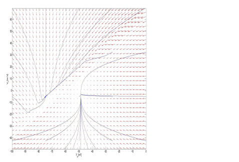
$$
\begin{aligned}
\dot{V}_i &= -\beta(V_i - V_e^r) + \sqrt{2}\sigma\dot{W}_i \\
\dot{V}_e &= -\alpha(V_e - V_e^r) + \sqrt{2}\sigma\dot{W}_e
\end{aligned}
$$

- Domain II: $V_e > V_i + \theta_e$

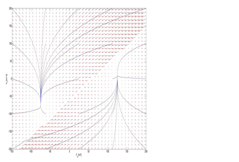
$$
\begin{aligned}
\dot{V}_i &= -\beta(V_i - V_e^r) + \beta_0 a_i S_{max} + \sqrt{2}\sigma\dot{W}_i \\
\dot{V}_e &= -\alpha(V_e - V_e^r) + \alpha a_e S_{max} + \sqrt{2}\sigma\dot{W}_e
\end{aligned}
$$

- Domain III ($V_e < V_i + \theta_e$ and $V_e > V_i + \theta_i$)

$$
\begin{aligned}
\dot{V}_i &= -\beta(V_i - V_e^r) + \beta_0 a_i S_{max} + \sqrt{2}\sigma\dot{W}_i \\
\dot{V}_e &= -\alpha(V_e - V_e^r) + \sqrt{2}\sigma\dot{W}_e
\end{aligned}
$$



Phase portrait in *Heaviside* functions case: $\theta_e > \theta_i$



Phase portrait in *Heaviside* functions case: $\theta_e = \theta_i = \theta$

Heaviside variant of the model: ranges of bi-stability

Heaviside functions case: $\theta_e = \theta_i = \theta$

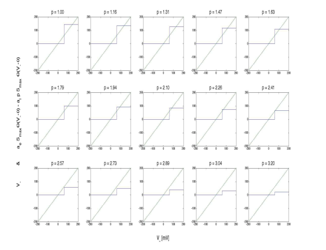
In order to determine the ranges of bi-stability in this variant of the model, it is needed to consider the following equation:

$$\overline{V}_- = a_e S_{max}\Theta(\overline{V}_- - \theta_e) - a_i p S_{max}\Theta(\overline{V}_- - \theta_i)$$

A first graphical analysis reveals that multiple interceptions of the l.h.s. term, the straight line $f(\overline{V}_-) = \overline{V}_-$, with the difference of the two scaled Heaviside functions on the r.h.s., are only possible in case of positive p values for (unrealistic) values of $\theta > 0$. In such a case the $\overline{V}_-$ coordinates of the fixed points are

$$
\begin{aligned}
\overline{V}_-^{(up)} &= (a_e - a_i p)S_{max} \\
\overline{V}_-^{(saddle)} &= \theta \\
\overline{V}_-^{(down)} &= 0
\end{aligned}
$$

and this simultaneous presence of two attractors occurs for p values bellow a critical one p_c: $p < p_c = \frac{a_e S_{max} - \theta}{a_i S_{max}}$. This does not exclude also unrealistic negative values for p.



Heaviside functions case: $\theta_e > \theta_i$

In this case, , for low values of p, the r.h.s. and the l.h.s. of the fixed points equation presented above always encounter in, at least, one ('up') attractor $\overline{V}_- > \theta_e$, located at the upper branch of the difference between the two scaled Heaviside functions (the r.h.s.):

$$\overline{V}_-^{(up)} = (a_e - a_i p)S_{max}$$

Only this attractor is present till a new interception appears when

$$-a_i p_c^{(1)} S_{max} = \theta_e \Longrightarrow p_c^{(1)} = \frac{-\theta_e}{a_i S_{max}}$$

that is, for $p \le p_c^{(1)}$ a mono-stable (excitable) regime is observed. More interceptions will appear with increasing values of p. A second critical value $p_c^{(2)}$ fixes the moment that the straight line $f(\overline{V}_-) = \overline{V}_-$ reaches the 'sliding' lower branch of the Heaviside functions difference:

$$a_e S_{max} - a_i p_c^{(2)} S_{max} = \theta_e \Longrightarrow p_c^{(2)} = \frac{-\theta_e + a_e S_{max}}{a_i S_{max}} = p_c^{(1)} + \frac{a_e}{a_i}$$

A bi-stable regime then exists for $p_c^{(1)} < p < p_c^{(2)}$ with two new fixed points:

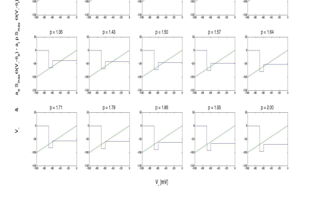
$$
\begin{aligned}
\overline{V}_-^{(up)} &= (a_e - a_i p)S_{max} \\
\overline{V}_-^{(saddle)} &= \theta_e \\
\overline{V}_-^{(down)} &= a_i p_c^{(2)} S_{max}
\end{aligned}
$$

The situation changes again when the moving difference reach the oblique line $f(\overline{V}_-) = \overline{V}_-$ at the lower neuronal threshold $\overline{V}_- = \theta_i$:

$$-a_i p_c^{(3)} S_{max} = \theta_i \Longrightarrow p_c^{(3)} = \frac{-\theta_i}{a_i S_{max}}$$

In this case the dynamics returns to a mono-stable regime with just one quiescent state $\overline{V}_-^{(down)} = \theta_i$ for every $p \ge p_c^{(3)}$.

Note: For the analysis above, we have assumed that $p_c^{(2)} < p_c^{(3)}$ or, equivalently, that $a_e S_{max} < \theta_e - \theta_i$.



A linear stability analysis

$$
\begin{aligned}
\dot{V}_i &= -\beta(V_i - V_e^r) + \beta a_i p S_i(V_- - \theta_i) + \sqrt{2}\sigma\dot{W}_i \\
\dot{V}_e &= -\alpha(V_e - V_e^r) + \alpha a_e S_e(V_- - \theta_e) + \sqrt{2}\sigma\dot{W}_e
\end{aligned}
$$

where $\beta = \beta_1 = \beta_0/p$ and $\alpha = \alpha_1$ and $V_- = V_e - V_i$ is the effective membrane potential.

$$J = \begin{bmatrix} N_i\beta & -(1+N_i)\beta \\ (-1+N_e)\alpha & -N_e\alpha \end{bmatrix}$$

with $\delta_e = \partial F_e/\partial V_-$ and $\delta_i = \partial F_i/\partial V_-$ evaluated at the fixed-point value $V_- = \overline{V}_-$. $N_e = a_e\delta_e$ and $N_i = a_i p\delta_i$

$$\lambda^2 - \lambda Tr + det = 0$$

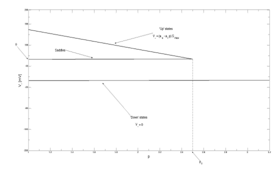
$$
\begin{aligned}
Tr &= \alpha(N_e - 1) - \beta(N_i + 1) \\
det &= \alpha\beta(N_i - N_e + 1)
\end{aligned}
$$

$$\lambda_{1,2} = \frac{1}{2}\left\{\alpha(N_e-1) - \beta(N_i+1) \pm \sqrt{\left[\alpha(N_e-1) + \beta(N_i+1)\right]^2 - 4\alpha\beta N_e N_i}\right\}$$

Heaviside case with $\theta_e \approxeq \theta_i = \theta$:

(a) $\overline{V}_- \approx \theta \Longrightarrow \delta_e \approx \frac{S_{max}}{4}c_e, \delta_i \approx \frac{S_{max}}{4}c_i : N_e \approx \frac{S_{max}}{4}c_e a_e, N_i \approx \frac{S_{max}}{4}c_i a_i p$

(b) $\overline{V}_- \neq \theta \Longrightarrow \delta_e \approx 0, \delta_i \approx 0 : N_e \approx 0, N_i \approx 0$
$\lambda_{1,2} = \frac{1}{2}\left\{-(\beta+\alpha) \pm \sqrt{(\beta-\alpha)^2}\right\} \Longrightarrow \lambda_1 = -\alpha, \lambda_2 = -\beta$

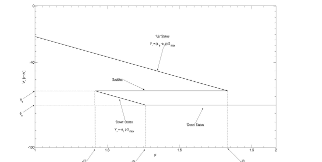


Heaviside case with $\theta_e \neq \theta_i$:

(a) $\overline{V}_- \approx \theta_e \Longrightarrow \delta_e \approx \frac{S_{max}}{4}c_e, \delta_i \approx 0 : N_e \approx \frac{S_{max}}{4}c_e a_e, N_i \approx 0 \Longrightarrow$
$\lambda_{1,2} = \frac{1}{2}\left\{\alpha(N_e-1) - \beta \pm \sqrt{[\alpha(N_e-1)+\beta]^2}\right\} \Longrightarrow \lambda_1 = \alpha(N_e-1) = \alpha\left(\frac{S_{max}}{4}c_e a_e - 1\right), \lambda_2 = -\beta$

(b) $\overline{V}_- \approx \theta_i \Longrightarrow \delta_i \approx \frac{S_{max}}{4}c_i, \delta_e \approx 0 : N_i \approx \frac{S_{max}}{4}c_i a_i p, N_e \approx 0 \Longrightarrow \lambda_{1,2} =$
$\frac{1}{2}\left\{-\alpha - \beta(N_i+1) \pm \sqrt{\left[-\alpha + \beta(N_i+1)\right]^2}\right\} \Longrightarrow \lambda_1 = -\alpha, \lambda_2 = -\beta(N_i+1) = -\beta\left(\frac{S_{max}}{4}c_i a_i p + 1\right)$

(c) $\overline{V}_- \neq \theta_e, \theta_i \Longrightarrow \delta_e \approx 0, \delta_i \approx 0 : N_e \approx 0, N_i \approx 0 \Longrightarrow \lambda_{1,2}$ Idem to case I.(b)



Conclusions: (1) Fixed points with values of $\overline{V}_-$ that considerable differ from the excitatory threshold value θ_e will correspond to stable nodes (2) Consequently, bifurcations in a curve p vs. $\overline{V}_-$ may only occur in the vicinity of $\overline{V}_- \sim \theta_e$ (3) Other kind of stable attractors, such as foci or unstable fixed points, such as saddles, will be located at that vicinity (4) The appearance of stable foci, however, can only be considered when $\theta_e \approxeq \theta_i = \theta$.

Fokker-Planck equation and FPT theory

Fokker-Planck equations for the probability density $P(V_i, V_e, t|V_i(0), V_e(0), 0) = P(V_e, V_i, t)$:

$$\frac{\partial P}{\partial t} = -\nabla \cdot \vec{J}$$

$$\vec{J} = \left(A_i P - \frac{B_i}{2}\frac{\partial P}{\partial V_i}, A_e P - \frac{B_e}{2}\frac{\partial P}{\partial V_e}\right)$$

with the drift coefficients A_i, A_e

$$
\begin{aligned}
A_i &= -\beta(V_i - V_e^r) + \beta a_i S_i(V_- - \theta_i) \\
A_e &= -\alpha(V_e - V_e^r) + \alpha a_e S_e(V_- - \theta_e)
\end{aligned}
$$

and diffusion terms $B_e = B_i = 2\sigma^2$. Additionally, appropriate Neumann boundary conditions (BCs) at the (reflecting) boundaries S defined by $V_i = \pm\infty$, $V_e = \pm\infty$ are needed:

$$\vec{n} \cdot \vec{J}(\vec{a}, t) = 0 \qquad for \qquad \vec{a} \in S$$

After replacing the Sigmoid firing-rate function S by a Heavise Θ, the drift terms turn into

$$
\begin{aligned}
A_i &= -\beta(V_i - V_e^r) + \beta a_i\Theta(V_- - \theta_i) \\
A_e &= -\alpha(V_e - V_e^r) + \alpha a_e\Theta(V_- - \theta_e).
\end{aligned}
$$

and the Fokker-Planck formalism can be split in other three equations coupled by exchange-currents of probability:

- Domain I ($V_e < V_i + \theta_i$)

$$\frac{\partial P_1}{\partial t} = -\frac{\partial}{\partial V_e}[A_e^{(1)}P_1] - \frac{\partial}{\partial V_i}[A_i^{(1)}P_1] + \frac{B_e}{2}\frac{\partial^2 P_1}{\partial V_e^2} + \frac{B_i}{2}\frac{\partial^2 P_1}{\partial V_i^2} - \nabla \cdot \vec{J}_{3,1}$$

$$
\begin{aligned}
A_i^{(1)} &= -\beta(V_i - V_e^r) \\
A_e^{(1)} &= -\alpha(V_e - V_e^r)
\end{aligned}
$$

$$\vec{J}_{3,1} = -\left(\frac{B_i}{2}\frac{\partial P_3}{\partial V_i}, \frac{B_e}{2}\frac{\partial P_3}{\partial V_e}\right)\delta(V_e - V_i - \theta_i)$$

- Domain II ($V_e > V_i + \theta_e$)

$$\frac{\partial P_2}{\partial t} = -\frac{\partial}{\partial V_e}[A_e^{(2)}P_2] - \frac{\partial}{\partial V_i}[A_i^{(2)}P_2] + \frac{B_e}{2}\frac{\partial^2 P_2}{\partial V_e^2} + \frac{B_i}{2}\frac{\partial^2 P_2}{\partial V_i^2} - \nabla \cdot \vec{J}_{3,2}$$

$$
\begin{aligned}
A_i^{(2)} &= -\beta(V_i - V_e^r) + \beta_0 a_i S_{max} \\
A_e^{(2)} &= -\alpha(V_e - V_e^r) + \alpha a_e S_{max}
\end{aligned}
$$

$$\vec{J}_{3,2} = -\left(\frac{B_i}{2}\frac{\partial P_3}{\partial V_i}, \frac{B_e}{2}\frac{\partial P_3}{\partial V_e}\right)\delta(V_e - V_i - \theta_e)$$

- Domain III ($V_e < V_i + \theta_e$ and $V_e > V_i + \theta_i$)

$$\frac{\partial P_3}{\partial t} = -\frac{\partial}{\partial V_e}[A_e^{(3)}P_3] - \frac{\partial}{\partial V_i}[A_i^{(3)}P_3] + \frac{B_e}{2}\frac{\partial^2 P_3}{\partial V_e^2} + \frac{B_i}{2}\frac{\partial^2 P_3}{\partial V_i^2} - \nabla \cdot \vec{J}_{2,3} - \nabla \cdot \vec{J}_{1,3}$$

$$
\begin{aligned}
A_i^{(3)} &= -\beta(V_i - V_e^r) + \beta_0 a_i S_{max} \\
A_e^{(3)} &= -\alpha(V_e - V_e^r)
\end{aligned}
$$

$$
\begin{aligned}
\vec{J}_{2,3} &= -\left(\frac{B_i}{2}\frac{\partial P_2}{\partial V_i}, \frac{B_e}{2}\frac{\partial P_2}{\partial V_e}\right)\delta(V_e - V_i - \theta_e) \\
\vec{J}_{1,3} &= -\left(\frac{B_i}{2}\frac{\partial P_1}{\partial V_i}, \frac{B_e}{2}\frac{\partial P_1}{\partial V_e}\right)\delta(V_e - V_i - \theta_i)
\end{aligned}
$$

The system above must be completed with suitable boundary and normalization conditions. For the sake of simplicity, from now on we focus in the simpler case $\theta_i = \theta_e = \theta$:

- Domain I ($V_e < V_i + \theta$)

$$\frac{\partial P_1}{\partial t} = -\frac{\partial}{\partial V_e}[A_e^{(1)}P_1] - \frac{\partial}{\partial V_i}[A_i^{(1)}P_1] + \frac{B_e}{2}\frac{\partial^2 P_1}{\partial V_e^2} + \frac{B_i}{2}\frac{\partial^2 P_1}{\partial V_i^2} + \nabla \cdot \vec{J}_0$$

- Domain II ($V_e > V_i + \theta$)

$$\frac{\partial P_2}{\partial t} = -\frac{\partial}{\partial V_e}[A_e^{(2)}P_2] - \frac{\partial}{\partial V_i}[A_i^{(2)}P_2] + \frac{B_e}{2}\frac{\partial^2 P_2}{\partial V_e^2} + \frac{B_i}{2}\frac{\partial^2 P_2}{\partial V_i^2} - \nabla \cdot \vec{J}_0$$

According to the computational simulations, escape mostly occurs through the points $V^{(exit)} = (V_i^{(exit)}, V_e^{(exit)})$ located at the border line $V_e - V_i - \theta = 0$ and closest to the attractors, that is,

$$
\begin{aligned}
V_i^{(exit)} &= \frac{V_i^s + V_i^s + \theta}{2} \\
V_e^{(exit)} &= \frac{V_i^s + V_i^s - \theta}{2}
\end{aligned}
$$

where $V_i^s = V_e^s = V_e^r$ are the ('down') attractor coordinates located in domain I and $V_i^s = V_e^r + a_i p S_{max}$, $V_e^s = V_e^r + a_e S_{max}$ the ('up') attractor coordinates placed in domain II. Hence J_0 can be approximated as a point current of probability through that point, and the partial derivatives may be evaluated just at $V = V^{(exit)}$:

$$J_0 = -\left(\frac{B_i}{2}\frac{\partial P_1}{\partial V_i}, \frac{B_e}{2}\frac{\partial P_1}{\partial V_e}\right)\delta\left(V_i - V_i^{(exit)}\right)\delta\left(V_e - V_e^{(exit)}\right)$$

Knowing the probability $P_s(V_i, V_e, t) = P_s(V_i, V_e, t|V_i(0), V_e(0), t=0) = P(V_e, V_i, t)$ makes possible the direct calculation of the probability $G(V_i, V_e)$ that the trajectory stays in each of the domains D_s for a maximum of time $t = T$:

$$G_s(V_i, V_e, t) = Prob(T \ge t) = \int_{D_s} dV_i' dV_e' P_s(V_i', V_e', t|V_i, V_e, 0)$$

Finally, the waiting time distribution $F_s(t)$ for each domain is given by

$$F_s(t) = -\frac{\partial G_s}{\partial t}$$

and the mean exit (or first-passage) time $T(V_i, V_e)$ can be obtained as

$$T_s(V_i, V_e) = \int_0^\infty tF_s(t)dt = \int_0^\infty G_s(V_i, V_e, t)dt$$

There are, however, alternative solutions to the original FPT problem. For instance, seems to be feasible the direct use of the PDEs for the time-integrated quantity $G_s(V_i, V_e, t)$, i.e., a backward Fokker-Planck equation:

$$\frac{\partial G_s}{\partial t} = A_e^{(s)}\frac{\partial G_s}{\partial V_e} + A_i^{(s)}\frac{\partial G_s}{\partial V_i} + \frac{B_e}{2}\frac{\partial^2 G_s}{\partial V_e^2} + \frac{B_i}{2}\frac{\partial^2 G_s}{\partial V_i^2}$$

with the appropriate BCs.

Avoiding an oblique boundary and the infinite integration domains in FPT theory: further transformations

- A 45°-rotation of the (V_i, V_e) coordinate system about the origin:

$$\begin{bmatrix}\hat{V}_+ \\ \hat{V}_-\end{bmatrix} = \frac{1}{\sqrt{2}}\begin{bmatrix}1 & 1 \\ -1 & 1\end{bmatrix}\begin{bmatrix}V_i \\ V_e\end{bmatrix} = \frac{1}{\sqrt{2}}\begin{bmatrix}V_+ \\ V_-\end{bmatrix}$$

- Domain I: $\hat{V}_- < \theta_i/\sqrt{2}$

$$\frac{d}{dt}\begin{bmatrix}\hat{V}_+ \\ \hat{V}_-\end{bmatrix} = \frac{1}{2}\begin{bmatrix}-(\beta+\alpha) & \beta-\alpha \\ \beta-\alpha & -(\beta+\alpha)\end{bmatrix}\begin{bmatrix}\hat{V}_+ \\ \hat{V}_-\end{bmatrix} + \frac{V_e^r}{\sqrt{2}}\begin{bmatrix}(\beta+\alpha) \\ -(\beta-\alpha)\end{bmatrix} + 2\sigma\begin{bmatrix}\dot{\eta}_+ \\ \dot{\eta}_-\end{bmatrix}$$

where $\eta_{\{+,-\}}$ are Wiener processes.

- Domain II: $\hat{V}_- > \theta_e/\sqrt{2}$

$$\frac{d}{dt}\begin{bmatrix}\hat{V}_+ \\ \hat{V}_-\end{bmatrix} = \frac{1}{2}\begin{bmatrix}-(\beta+\alpha) & \beta-\alpha \\ \beta-\alpha & -(\beta+\alpha)\end{bmatrix}\begin{bmatrix}\hat{V}_+ \\ \hat{V}_-\end{bmatrix} + \frac{1}{\sqrt{2}}\begin{bmatrix}(\beta+\alpha)V_e^r + (\beta_0 a_i + \alpha a_e)S_{max} \\ -(\beta-\alpha)V_e^r + (-\beta_0 a_i + \alpha a_e)S_{max}\end{bmatrix} + 2\sigma\begin{bmatrix}\dot{\eta}_+ \\ \dot{\eta}_-\end{bmatrix}$$

- A non-linear transformation: $X_+ = \tanh\hat{V}_+$, $X_- = \tanh\hat{V}_-$. New Langevin equations are obtained with Ito's calculus :

$$
\begin{aligned}
\frac{dX_+}{dt} &= (1 - X_+^2)[C_+ - (2\sigma)^2 X_+] + 2\sigma(1 - X_+^2)\dot{\eta}_+ \\
\frac{dX_-}{dt} &= (1 - X_-^2)[C_- - (2\sigma)^2 X_-] + 2\sigma(1 - X_-^2)\dot{\eta}_-
\end{aligned}
$$

where

$$
\begin{aligned}
C_+ &= -\frac{\beta+\alpha}{4}\ln\left(\frac{1+X_+}{1-X_+}\right) + \frac{\beta-\alpha}{4}\ln\left(\frac{1+X_-}{1-X_-}\right) + \frac{\beta+\alpha}{\sqrt{2}}V_e^r + \frac{\beta_0 a_i + \alpha a_e}{\sqrt{2}}S_{max} \\
C_- &= \frac{\beta-\alpha}{4}\ln\left(\frac{1+X_+}{1-X_+}\right) - \frac{\beta+\alpha}{4}\ln\left(\frac{1+X_-}{1-X_-}\right) + \frac{-\beta+\alpha}{\sqrt{2}}V_e^r + \frac{-\beta_0 a_i + \alpha a_e}{\sqrt{2}}S_{max}
\end{aligned}
$$

Fokker-Planck equation:

$$\frac{\partial P}{\partial t} = -\frac{\partial}{\partial X_s}[A_s P] - \frac{\partial}{\partial X_-}[A_- P] + \frac{B_{++}}{2}\frac{\partial^2 P}{\partial X_+^2} + \frac{B_{--}}{2}\frac{\partial^2 P}{\partial X_-^2}$$

where $P = P(X_+, X_-, t|X_+(0), X_-(0))$ is the conditional probability, and

$$
\begin{aligned}
A_s &= (1 - X_s^2)[C_s - (2\sigma)^2 X_s] \\
B_{ss} &= [2\sigma(1 - X_s^2)]^2
\end{aligned}
$$

are the drift and diffusion coefficients, respectively, with $s \in \{+, -\}$.

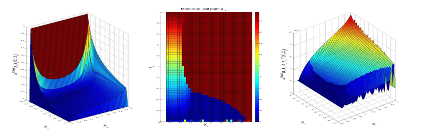
FPT equations: Exit probability $\pi(a_+, a_-|X_+, X_-)$ and mean point-exit time $\pi(a_+, a_-|X_+, X_-)T(a_+, a_-|X_+, X_-)$

$$\hat{F}\pi(a_+, a_-|X_+, X_-) = 0$$

$$\hat{F}\left[\pi(a_+, a_-|X_+, X_-)T(a_+, a_-|X_+, X_-)\right] = -\pi(a_+, a_-)$$

where $\hat{F}$ is the operator

$$\hat{F} = A_+\frac{\partial}{\partial X_+} + A_-\frac{\partial}{\partial X_-} + \frac{1}{2}B_{++}\frac{\partial^2}{\partial X_+^2} + \frac{1}{2}B_{--}\frac{\partial^2}{\partial X_-^2}$$

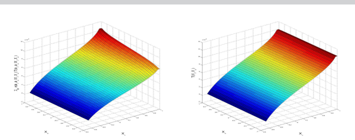


. Dirichlet BCs at the saddles (absorbing) line $V_e - V_i - \theta_e/\sqrt{2} = 0$: $\pi(a_+, a_-|a_+, a_-) = 1$, $T(a_+, a_-|a_+, a_-) = 0$, and in the remainder (reflecting) boundaries: $\pi(a_+, a_-|X_+, X_-) = 0$

. Neumann BCs at the remainder (reflecting) boundaries: $\frac{\partial}{\partial X_s}\left[\pi(a_+, a_-|X_+, X_-)T(a_+, a_-|X_+, X_-)\right] = 0$.

FPT equations: total point-exit time $\sum_a \pi(a_+, a_-|X_+, X_-)T(a_+, a_-|X_+, X_-)$ and global mean exit time $T(X_+, X_-)$

$$\hat{F}T(X_+, X_-) = -1$$



. Dirichlet BCs at the saddles (absorbing) line $V_e - V_i - \theta_e/\sqrt{2} = 0$: $T(X_+, X_-) = 0$.
. Neumann BCs at the remainder (reflecting) boundaries: $\frac{\partial}{\partial X_s}T(X_+, X_-) = 0$.

Computational simulations